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TITLE: Preparation of Bulk Drug for the U.S. Army Drug Development Program

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13. ABSTRACT (Maximum 200 Words)
The following four compounds were synthesized:
2H-Pyrido[2, 3-d][1,3]oxazine-2,4(1H)-dione; Pyrido[2', 3':4, 5] pyrimido [1, 2-a]indole-5, 11-dione, 9-methoxy-; pyrido[2', 3':4, 5]pyrimido[1, 2-a]indole-5, 11-dione, 9-hydroxy-; 1-(5, 11-dioxo-5,11-dihydropyrido[2', 3':4, 5]-pyrimido[1, 2-a]indol-9-yl) hemisuccinate.

14. SUBJECT TERMS
Hydroxy-aza-tryptanthrin; Pyrido[2', 3':4, 5]pyrimido-[1, 2-a]indole-5, 11-dione derivatives.

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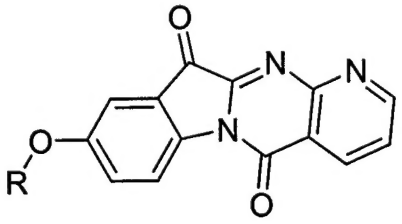
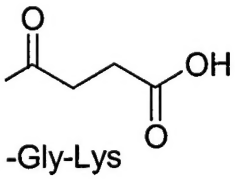
Introduction

The Final Report for the subject contract was submitted during March 2003 for the work period February 15, 1999 - February 14, 2003. That Final Report summarized work performed under tasks 1-7. The subject contract was subsequently extended for a one-year period with research to be completed by February 14, 2004. In conjunction with this extension, task 8 was assigned. The present Addendum to the Final Report describes in detail the research carried out under task 8 through the work period ending February 14, 2004.

The task 8 assignment of this contract was to undertake the non-cGMP synthesis of two or more of the target compounds shown below:



I: R= 

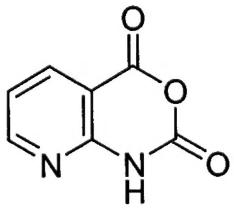
II: R= -Gly-Lys

III: R= -Gly-His

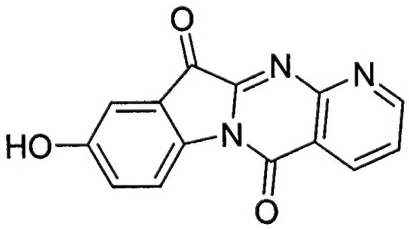
IV: R= -Gly-Arg

V: R= -Gly-Arg-Arg

Task 8 also provided for the potential shipment of one or both of the following two key synthetic intermediates, upon request by WRAIR:



VI



VII

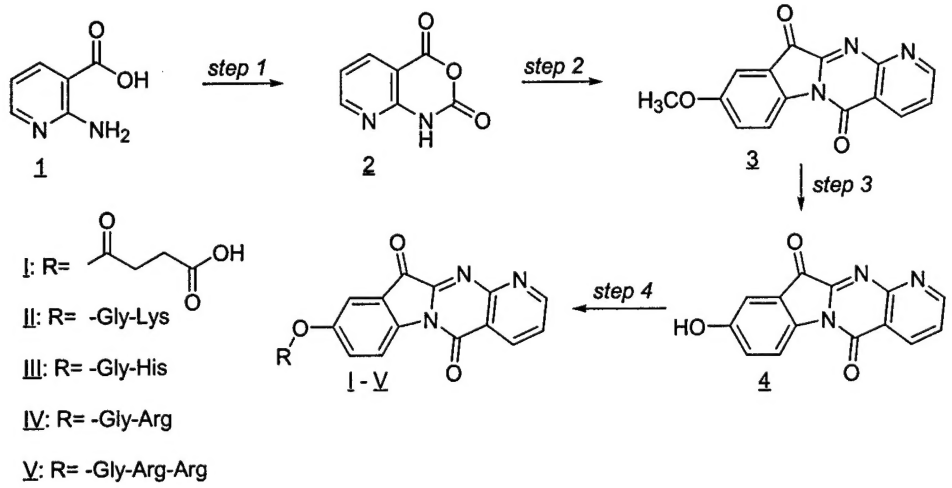
Body

RESEARCH AND KNOWN TARGET COMPOUNDS COMPLETED AND DELIVERED TO WALTER REED ARMY INSTITUTE OF RESEARCH FROM FEBRUARY 15, 1999 TO FEBRUARY 14, 2004

The experimental details for all materials prepared under task order assignments 1, 2, and 3 have been described in our Annual Report dated March 2000, pp. 2-95. Materials prepared under task order assignments 4 and 5 have been described in our Annual Report dated March 2001, pp. 2-9. Materials prepared under task order assignment 6 have been described in our Annual Report dated March 2002, pp. 2-10. The experimental details for task order assignment 7 have been described in our Final Report dated March 2003, pp. 2-26. The experimental details for task order assignment 8 are described in the following pages.

Overview

The following four-step sequence of reactions was envisioned for the synthesis of target compounds I-V.



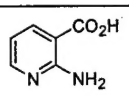
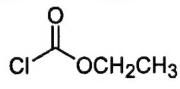
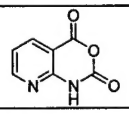
Target compounds I-V may be considered as water-solubilizing prodrugs of hydroxy-aza-tryptanthrin, 4. Compound 4 shows negligible to low solubility in water and also in most organic solvents. The bulk of this contractor's efforts under task 8 were devoted to synthesis and purification of 4. Compound 4 was successfully isolated in essentially pure form at the 200 mg scale as demonstrated by proton NMR, mass spec, and C,H,N analyses. A small amount of target hemisuccinate ester I was also prepared in crude form as demonstrated by mass spec and NMR.

Additional efforts towards targets I-V and/or other derivatives of 4 may continue, as the National Institute of Allergy and Infectious Diseases (NIAID) has expressed interest in the project. WRAIR will leverage its resources developed under task 8 in conjunction with NIAID's interest. Any resultant compounds are expected to be shared between NIAID and WRAIR.

Step 1: Conversion of 1 to 2

The first step was carried out three times to give a total of 98.7 g of 2H-pyrido[2,3-*d*][1,3]-oxazine-2,4(1H)-dione:

Reaction Trials for Step 1

TRIAL			
#1	146 g	3250 mL	20.3 g
#2	175 g	3000 mL	28.5 g
#3	175 g	3000 mL	49.9 g

Step 2: Preparation of 3

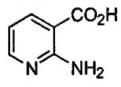
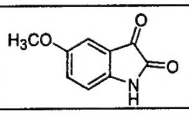
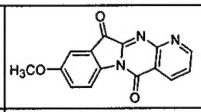
Eleven reactions were run in scouting the second step. Three different methods were attempted, all of which involved coupling either 1 or 2 with 5-methoxyisatin.

Method 'A' used 2-aminonicotinic acid (1) directly (instead of the anhydride 2), along with *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (HBTU), 4-methylmorpholine (NMM), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

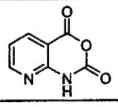
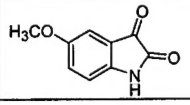
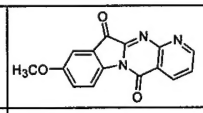
Method 'B' used 1,3-diisopropylcarbodiimide (DIC), 1-methyl-2-pyrrolidinone (NMP), and pyridine (PYR) as the reagents for coupling.

Method 'C' involved coupling with 4-(dimethylamino)-pyridine (DMAP) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in *N*,*N*-dimethylformamide (DMF).

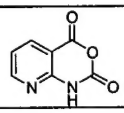
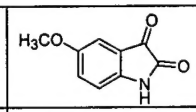
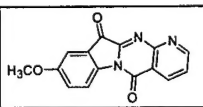
Reaction Trials for Step 2 (Method A)

TRIAL			HBTU	NMM	DBU	
#1	1.0 g	1.2 g	2.8g	1.5mL	2.5mL	400 mg
#2	10.4 g	12.1 g	28.5g	15mL	25mL	1.9 g
#3	9.1 g	10.6 g	25.0g	12g	22.3g	2.4 g

Reaction Trials for Step 2 (Method B)

TRIAL			DIC	NMP	PYR	
#4	5.0 g	5.4 g	3.8g	107mg	25mL	1.2 g
#5	3.6 g	3.8 g	2.2mL	86µL	20mL	3.3 g
#6	9.3 g	10.0 g	5.8mL	225µL	50mL	2.9 g
#7	18.0 g	19.4 g	11.3mL	435µL	100mL	5.7 g
#8	9.3 g	10.0 g	8.8mL	225µL	50mL	6.3 g
#9	9.3 g	10.0 g	5.8mL	225µL	50 mL	6.6 g

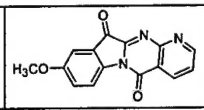
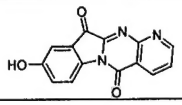
Reaction Trials for Step 2 (Method C)

TRIAL			DMAP	DBU	DMF	
#10	2.40 g	2.35 g	160mg	2.22g	100mL	1.5 g
#11	10.4 g	12.1g	28.5g	15mL	25mL	1.9 g

Step 3: Conversion of 3 to 4

Demethylation of the methyl ether was attempted twelve times using either boron tribromide or hydrogen bromide. In all cases, the product proved difficult to purify. However, a reasonable purification method was developed which included repeated crystallization of the crude material from DMF, followed by washing the dark red crystals of 4 with methanol. Elemental and ^{1}H NMR analyses were obtained which, although indicating the presence of a small amount of DMF and methanol confirmed the success of the purification process.

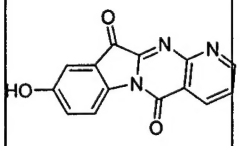
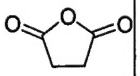
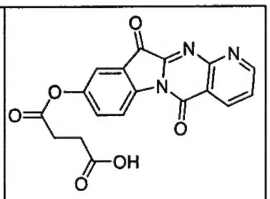
Reaction Trials for Step 3

TRIAL		BBr_3 (1M)	HBr (45%)	
#1	279 mg	2 mL	-	210 mg (crude)
#2	279 mg	2 mL	-	150 mg (crude)
#3	740 mg	5.3 mL	-	410 mg (crude)
#4	400 mg	3 mL	-	230 mg (crude)
#5	1.24 g	9 mL	-	550 mg (crude)
#6	1.22 g	8.8 mL	-	NA
#7	500 mg	3.6 mL	-	450 mg (crude)
#8	1.95 g	14 mL	-	1.8 g (crude)
#9	500 mg	3.6 mL	-	200 mg (crude)
#10	10.3 g	75 mL	-	5.1 g (crude)
#11	2.2 g	10 mL	-	1.1 g (crude)
#12	270 mg	-	10 mL	decomp.

Step 4: Conversion of 4 to 5

The hemisuccinate was prepared using succinic anhydride. Five different attempts revealed the desired product to be quite labile. Presumably, the free acid functional group helps catalyze the hydrolysis of the aromatic ester group to revert to the starting material.

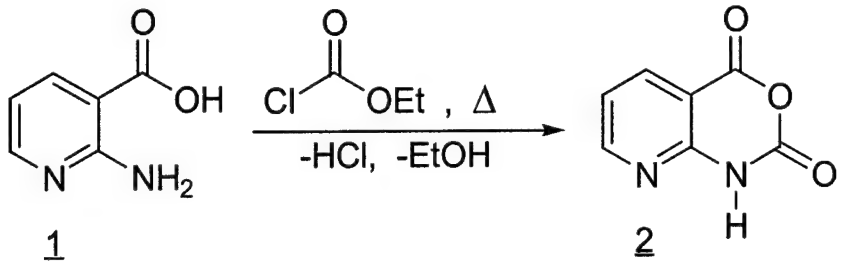
Reaction Trials for Step 4

TRIAL			NaH	DMAP	Et_3N	
#1	200 mg	226 mg	-	39 mg	350 µL	130 mg (crude)
#2	100 mg	40 mg	-	-	-	no rxn
#3	100 mg	40 mg	15 mg	-	-	30 mg (crude)
#4	100 mg	46 mg	-	-	-	no rxn
#5	100 mg	184 mg	-	30 mg		20 mg (crude)

Selected Experimental Procedures

Step 1: Conversion of 1 to 2

Compound 2 was prepared by the following reaction:



1 2

A stirred suspension of 2-aminonicotinic acid (1) (175 g, 1.27 mol) in ethyl chloroformate (2 kg initially, but 3 kg overall for a 27.6 mol total) was heated in a 100°C oil bath, and allowed to reflux for six hours. Additional ethyl chloroformate (5 x 100 g) was added, portionwise over 6h, in order to thin the reaction mixture. The reaction was returned to RT, stirred overnight, then reheated to reflux for an additional six hours - again adding additional ethyl chloroformate (5 x 100 g), portionwise over 6h, in order to thin the reaction mixture. A distillation head was attached, and ~1 kg of distillate was removed from the reaction mixture before cooling to RT. The mixture was diluted with 1L chloroform, stirred for 30 min., and the solids were collected on a filter and rinsed with an additional 500 mL $CHCl_3$ to give a mixture of target, 2-aminonicotinic acid hydrochloride, and a small amount of 2-aminonicotinic acid. These solids were sequentially washed with water (1L), 0.3N aq. HCl (500 mL), water (3x500 mL), and finally with chloroform (500 mL) to remove the starting material (free-base and salt form). The pure target was dried in vacuo at 50°C to give 49.9 g (35% yield based on recovered starting material.

Starting material 1 was recovered by treating the combined aqueous filtrates with 5% aqueous sodium hydroxide to give pH=5.5, collecting the precipitate, washing with water, and drying in vacuo at 60°C to give 55 g of 2-aminonicotinic acid.

Elemental Analysis

164.12 g/mole	%C	%H	%N
$C_7H_4N_2O_3$	51.23	2.46	17.07
Found	51.15	2.49	17.02

Spectral Data

Nuclear Magnetic Resonance (DMSO-d_6)

δ 12.28 (s, 1H, N-H); 8.65 (dd, 1H, J=4.8 & 1.8 Hz, H-5); 8.31 (dd, 1H, J=7.8 & 1.8 Hz, H-7); 7.31 (dd, 1H, J=7.8 & 4.8 Hz, H-6) at 600 MHz. D_2O exchanged one proton at 12.28 ppm.

Thin Layer Chromatography

EM precoated, glass TLC plates (0.25 x 50 x 100 mm, SiO_2 60F-254). Detection: UV light and iodine vapor.

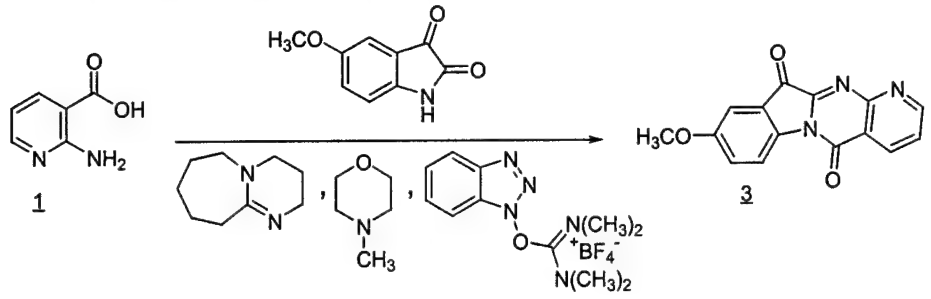
Eluent	Rf value
1) EtOAc	0.71
2) EtOAc/MeOH (2:1)	0.80

Reverse-phase plates (J.T. Baker #1013-00, C_{18})

Eluent	Rf value
1) MeOH/H_2O (3:2)	0.60

Step 2: Preparation of 3 (Method A)

Compound 3 was prepared by the following reaction:



To a solution of *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (HBTU) (28.5g, 75.1 mmol), 4-methylmorpholine (NMM) (15 mL, 136 mmol), and 2-aminonicotinic acid (1) (10.4 g, 75.3 mmol) in 500 mL anhyd. DMF was added a solution of 5-methoxyisatin (12.1 g, 68.3 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (25 mL, 167 mmol) in 400 mL anhyd. DMF over 15 min. After stirring for 24h at RT, the reaction mixture was quenched with aq. citric acid (2L of 1N). Additional water was added to give a final, total volume of 10L. Insolubles were removed by filtration and discarded. The filtrate was extracted with chloroform (5x1L). The combined extracts were washed with water (2x3L), dried (Na_2SO_4), filtered and spin-evaporated. The residue was purified by chromatography (1.2 kg SiO_2 eluted with a CH_2Cl_2-EtOAc gradient from 10:1 to 1:1) to give 1.92 g (10.1% yield) of 3.

Elemental Analysis

279.3 g/mole	%C	%H	%N
$C_{15}H_9N_3O_3$	64.52	3.25	15.05
Found	64.36	3.20	15.22

Spectral Data

Nuclear Magnetic Resonance (DMSO-d_6)

^1H δ 9.06 (1H, dd, J=1.9 & 4.5 Hz); 8.68 (1H, dd, J=1.9 & 7.8 Hz); 8.34 (1H, m); 7.74 (1H, dd, J=4.6 & 7.9 Hz); 7.45 (1H, s); 7.44 (1H, m); 3.88 (3H, s) at 600 MHz.

Nuclear Magnetic Resonance (DMSO-d_6)

^{13}C δ 158.2, 157.6, 157.1, 155.9, 139.6, 136.1, 131.7, 124.6, 123.8, 123.3, 119.2, 118.1, 108.7, 56.0 at 125 MHz. One resonance was not resolved from the noise.

FT-Infrared

ν 3081, 2944, 2847, 1742, 1687, 1620, 1587, 1491, 1467, 1442, 1413, 1358, 1306, 1287, 1243, 1193, 1155, 1087, 1056, 1016, 947, 897, 825, 789, 721, 707, 665, 549, 483 cm^{-1}.

Mass (TOF MS EI^+)

Exact mass of $C_{15}H_9N_3O_3$ = 279.0644

Found: 279.1 (100%)

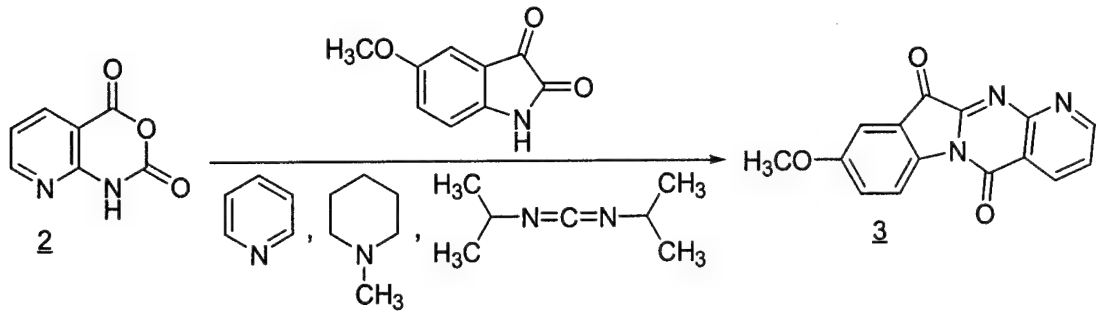
Thin Layer Chromatography

EM precoated, glass TLC plates (0.25 x 50 x 100 mm, SiO_2 60F-254). Detection: UV light and iodine vapor.

Eluent	Rf value
1) CH_2Cl_2-MeOH (19:1)	0.51
2) CH_2Cl_2-EtOAc (2:1)	0.27

Step 2: Preparation of 3 (Method B)

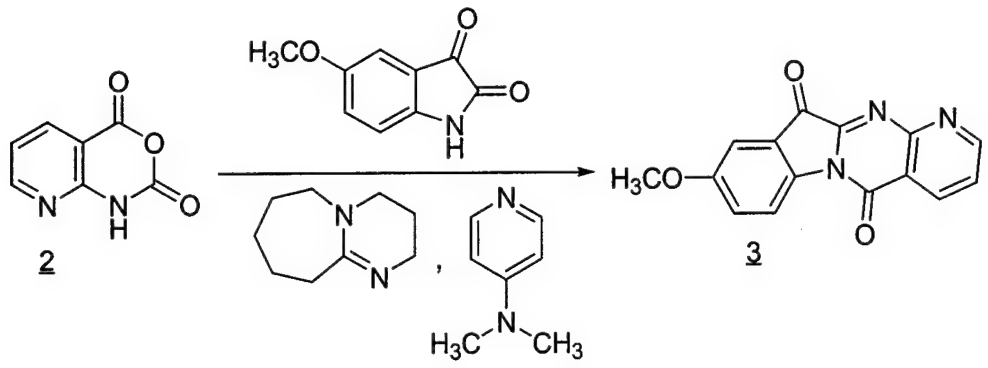
Compound 3 was prepared by the following reaction:



A solution of N-methylpiperidine (225 µL, 2.15 mmol) and diisopropylcarbodiimide (5.8 mL, 37.46 mmol) in pyridine (50 mL) was heated under argon to 60°C. 5-Methoxyisatin (10.0 g, 56.45 mmol) and 2H-pyrido[2,3-*d*][1,3]oxazine-2,4(1H)-dione (2) (9.3 g, 56.67 mmol) were added as solids, then the reaction mixture was heated to 100°C. After 30 min., the mixture was cooled to RT and diluted with water (500 mL). The insolubles were collected on a filter, rinsed with additional water (2x100 mL), and dried in vacuo to give 6.6g of crude 3. The crude material was suspended in chloroform (600 mL), stirred for one hour, then filtered. The filtrate was spin-evaporated, then purified by chromatography (300 g SiO_2 eluted with a CH_2Cl_2-EtOAc 3:1). Fractions containing product were combined and spin-evaporated. The orange solid was triturated with ether (25 mL), then dried in vacuo to give pure 3; mp 240-244°C. See 'Method A' for spectral data and TLC behavior.

Step 2: Preparation of 3 (Method C)

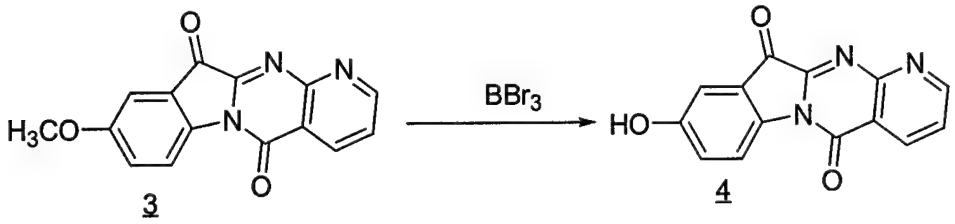
Compound 3 was prepared by the following reaction:



5-Methoxyisatin (2.35 g, 13.3 mmol) and 2H-pyrido[2,3-*d*][1,3]oxazine-2,4(1H)-dione (2) (2.40 g, 14.6 mmol) were dissolved in *N,N*-dimethylformamide (100 mL), then a solution of 4-(dimethylamino)pyridine (DMAP) (0.16 g, 1.3 mmol) in 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.22g, 14.6 mmol) was added, dropwise, over five minutes. The reaction flask was fitted with a $CaSO_4$ drying tube, and the reaction mixture was stirred at RT for 65h. Aqueous HCl was added (150 mL of 0.24M), and the mixture was stirred for 2h. After leaving the reaction mixture undisturbed for an additional 2h, the precipitate was collected on a filter and dried in vacuo to give 1.5 g of 3. See 'Method A' for spectral data and TLC behavior.

Step 3: Conversion of 3 to 4

Compound 4 was prepared by the following reaction:



A stirred solution of 3 in chloroform (1.95 g, 6.98 mmol in 50 mL) was cooled in an ice bath under argon before a solution of BBr_3 in CH_2Cl_2 (14 mL of 1M) was added dropwise. The reaction mixture was kept at 0°C for 1h, then stirred at RT for 16h. Water (25 mL) was added, and the mixture was stirred for 15 min. Insolubles were collected on a filter, washed with water (2x25 mL), chloroform (2x25 mL), and methanol (25 mL), then dried in vacuo to give 1.8 g of crude 4. This was dissolved in hot DMF (35 mL), filtered, and allowed to crystallize overnight. The crystals were collected, rinsed with methanol, then recrystallized once more from DMF to give 0.32 g (18%) of 4; mp. >370°C. A 10 mg portion (lot number 2N8-42-2) was transmitted to WRAIR on 24 February 2004.

Elemental Analysis ($C_{14}H_7N_3O_3$ + 0.15 MeOH + 0.15 DMF)

	%C	%H	%N
Calculated	62.41	3.10	15.70
Found	62.11	2.82	15.41

Spectral Data

Nuclear Magnetic Resonance (DMSO-d_6)

^1H δ 10.27 (1H, s); 9.04 (1H, dd, J=3.9 & 5.9 Hz); 8.67 (1H, dd, J=1.9 & 7.9 Hz); 8.25 (1H, d, J=8.6 Hz);

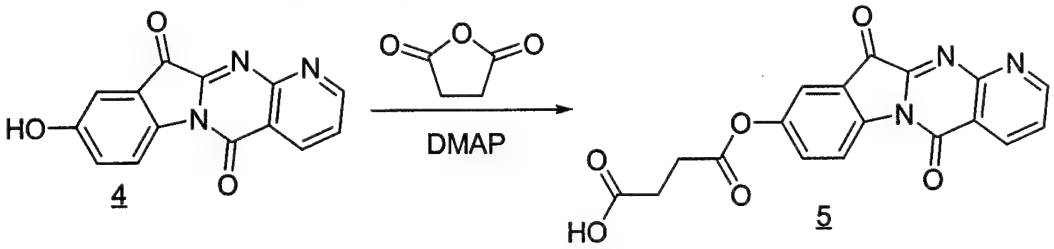
7.72 (1H, dd, J=4.5 & 7.9 Hz); 7.24 (1H, dd, J=2.6 & 8.6 Hz); 7.17 (1H, d, J=2.5 Hz) at 600 MHz.

Thin Layer Chromatography

EM precoated, glass TLC plates (0.25 x 50 x 100 mm, SiO_2 60F-254). Detection: UV light and iodine vapor. CH_2Cl_2-MeOH (9:1) Rf=0.56

Step 4: Conversion of 4 to 5

Compound 5 was prepared by the following reaction:



4 5

A solution of 4 in anhyd. DMF (100 mg, 0.38 mmol in 15 mL) was treated with 4-(dimethylamino)pyridine (10 mg, 0.08 mmol) followed by solid succinic anhydride (92 mg, 0.92 mmol). The mixture was heated to 60°C for 1h. Additional portions of 4-(dimethylamino)pyridine (20 mg) and succinic anhydride (92 mg) were added, and the mixture was heated to 60°C for another hour. After cooling to RT, the reaction was stirred overnight. Insolubles were removed by filtration, then the filtrate was spin-evaporated. The residue was stirred with methanol (20 mL), then the insolubles were removed by filtration and the filtrate was spin-evaporated. The residue was triturated with CH_2Cl_2 and dried in vacuo to give 20 mg of target 5.

Mass Spectrum (ES^-)

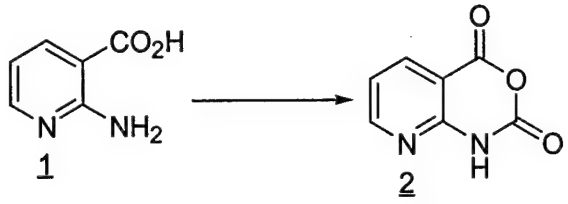
Exact mass of $C_{18}H_{11}N_3O_6$ = 365.0648

Found: 364.3 [M-1]

Key Research Accomplishments

- 2H-Pyrido[2,3-*d*][1,3]oxazine-2,4(1H)-dione (2)

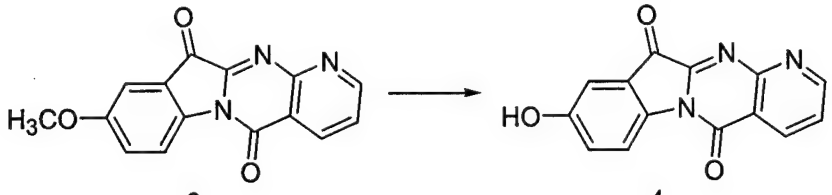
We prepared a total of 98.7 g of 2 from 2-aminonicotinic acid (1).



1 2

- 5,11-Dihydropyrido[2',3':4,5]pyrimido[1,2-a]-indole-5,11-dione, 9-hydroxy- (4)

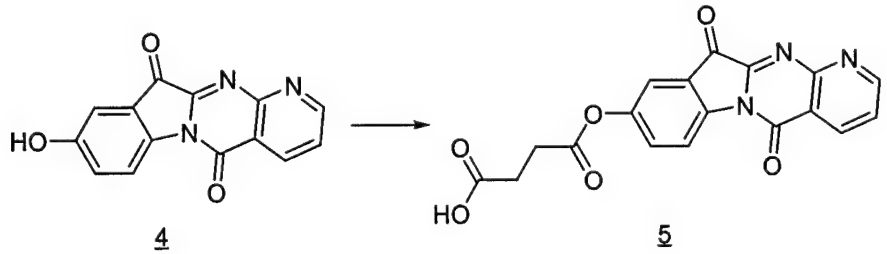
Key intermediate 4 was successfully synthesized and purified. A 10 mg portion was transmitted to WRAIR.



3 4

- 1-(5,11-Dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indol-9-yl) hemisuccinate (5)

Target compound 5 was prepared in crude form. Mass spectral analysis confirmed the presence of the molecular ion.



4 5

Conclusions

CUMULATIVE LIST OF REQUESTED COMPOUNDS DELIVERED TO WALTER REED ARMY INSTITUTE OF RESEARCH (WRAIR) FROM FEBRUARY 15, 1999 TO FEBRUARY 14, 2004

The current list of compounds delivered to WRAIR continues the cumulative numbering initiated with Starks' earliest contract with WRAIR. This list includes compounds numbered 1257 to 1283. Earlier lists, which described compounds 1 to 1256, may be found in the following reports:

Period of Final Summary Report	Contract No.	Page
February 15, 1999 to February 14, 2003	DAMD17-99-D-0005	p. 17
December 1, 1992 to March 31, 1999	DAMD17-93-C-3003	p. 48
March 15, 1989 to November 30, 1992	DAMD17-89-C-9058	p. 35
September 15, 1983 to March 14, 1989	DAMD17-83-C-3206	p. 55
September 29, 1979 to September 14, 1983	DAMD17-79-C-9170	p. 56
July 1, 1973 to September 28, 1979	DAMD17-73-C-3159	p. 82
July 1, 1965 to June 30, 1973	DA49-193-MD-2751	p. 54

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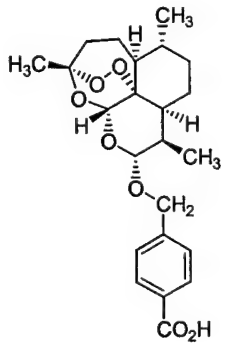
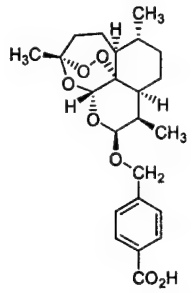
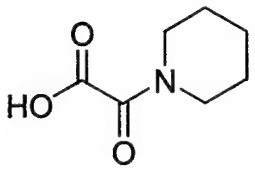
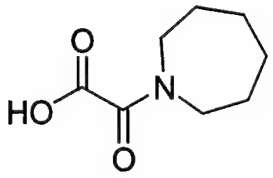
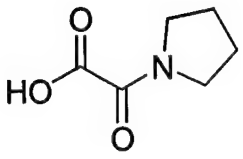
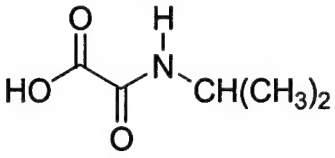
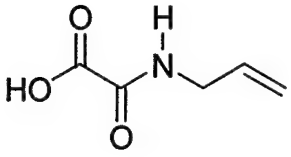
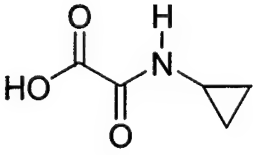
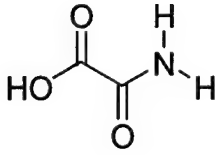
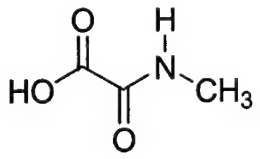
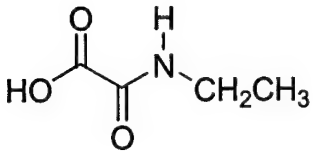
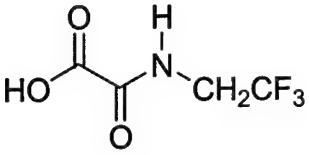
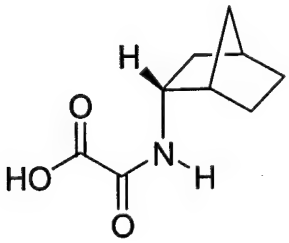
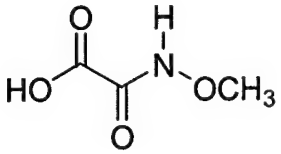
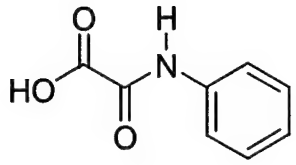
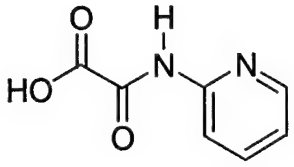
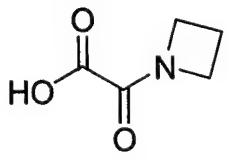
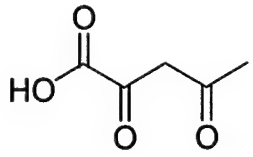
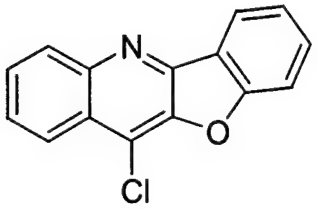
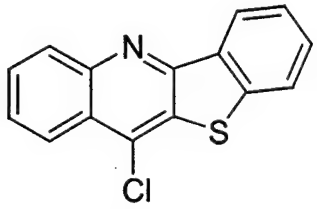
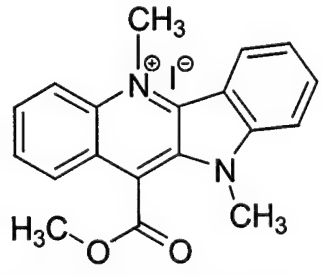
					
1257	α-Artelinic acid	438.6 g	BP14995	282644	137

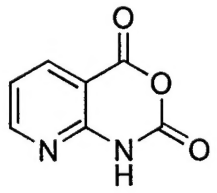
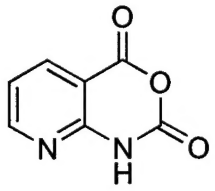
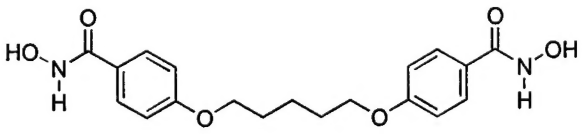
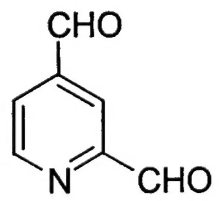
Cumulative No.	Compound	Amount	BN#	WR#	Starks Assoc. Report
					
1258	β-Artelinic acid, hemihydrate (cGMP)	1871.0 g	BP15009	255663	137
					
1259	1-Piperidineacetic acid, .alpha.-oxo-	2.1 g	BP15634	282987	137
					
1260	1*H*-Azepine-1-glyoxylic acid, hexahydro-	3.4 g	BP20500	283159	137
					
1261	1-Pyrrolidine-acetic acid, .alpha.-oxo-	1.8 g	BP15625	282986	137

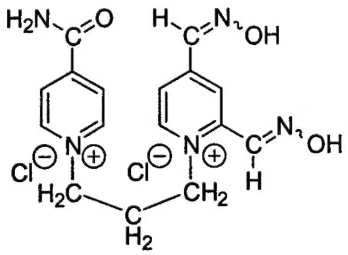
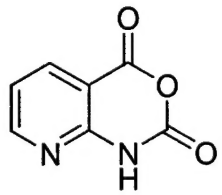
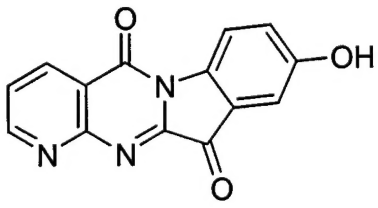
Cumulative No.	Compound	Amount	BN#	WR#	Starks Assoc. Report
					
1262	Acetic acid, [(1-methylethyl)-amino]oxo-	2.7 g	BP15607	282984	137
					
1263	Acetic acid, oxo-(2-propenylamino)-	2.5 g	BP15590	282983	137
					
1264	Acetic acid, (cyclopropyl-amino)oxo-	0.5 g	BP15616	282985	137
					
1265	Acetic acid, aminooxo-	2.0 g	BP15858	11658	138

Cumulative No.	Compound	Amount	BN#	WR#	Starks Assoc. Report
					
1266	Acetic acid, (methylamino)oxo-	0.75 g	BP15849	283002	138
					
1267	Acetic acid, (ethylamino)oxo-	1.0 g	BP15830	283001	138
					
1268	Acetic acid oxo-[(2,2,2-trifluoro-ethyl)amino]-	1.06 g	BP15821	283000	138
					
1269	Acetic acid, [(bicyclo[2.2.1]-hept-2-yl)amino]-oxo-, *endo*-	0.88 g	BP15812	282999	138

Cumulative No.	Compound	Amount	BN#	WR#	Starks Assoc. Report
					
1270	Acetic acid, (methoxyamino)oxo-	0.988 g	BQ35462	288981	138
					
1271	Acetic acid, oxo-(phenylamino)-	0.856 g	BQ35471	032862	138
					
1272	Acetic acid, oxo(2-pyridinylamino)-	2.3 g	BQ35480	288982	138
					
1273	1-Azetidineacetic acid, .alpha. -oxo-	0.70 g	BQ35499	288983	138

Cumulative No.	Compound	Amount	BN#	WR#	Starks Assoc. Report
					
1274	Pentanoic acid, 2,4-dioxo-	0.301 g	BQ35506	288984	138
					
1275	Benzofuro[3,2-*b*]-quinoline, 11-chloro-	6.1 g	BP16533	283023	138
					
1276	[1]Benzothieno-[3,2-*b*]quinoline, 11-chloro-	12.9 g	BP16524	283022	138
					
1277	10*H*-Quindolinium, 11-(methoxycarbonyl)-5,10-dimethyl-, iodide	3.4 g	BP17941	283104	139

Cumulative No.	Compound	Amount	BN#	WR#	Starks Assoc. Report
					
1278	2H-Pyrido[2,3-*d*]-[1,3]oxazine-2,4-(1H)-dione	16.5 g	BP2000	283144	141
					
1279	2H-Pyrido[2,3-*d*]-[1,3]oxazine-2,4-(1H)-dione	90.0 g	BP21310	283144	141
					
1280	Benzamide, 4,4'-[1,5-pentanediylbis-(oxy)]bis[N-hydroxy-	140 mg	BP21472	283189	142
					
1281	Pyridine-2,4-di-carboxaldehyde	20.9 g	BP23798	283299	146

Cumulative No.	Compound	Amount	BN#	WR#	Starks Assoc. Report
					
1282	Pyridinium, 1-[3-[4-(aminocarbonyl)pyridinio]propyl]-2,4-bis[(hydroxyimino)-methyl]-, dichloride	4.0 g	BP84666	259584	147
					
1283	2H-Pyrido[2,3-*d*]-[1,3]oxazine-2,4(1H)-dione	111.5 g	BQ33806	283144	150
					
1284	Pyrido[2',3':4,5]-pyrimido[1,2-a]-indole-5,11-dione, 9-hydroxy-	10 mg	BQ91255	289022	*this report*

Appendices

ACKNOWLEDGEMENT

The following technical personnel were assigned to syntheses which have been requested by Walter Reed Army Institute of Research: Dr. J.F. Novotny (Supervisor), Dr. S.K. Chadda, Dr. J.W. Givens, Dr. L. Hsiao.

We would like to acknowledge the technical help of Mr. William Ellis.

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